






**GB1297476****Publication number:** GB1297476**Publication date:** 1972-11-22**Inventor:****Applicant:****Classification:**

**- international:** A61K9/16; A61K9/50; B01J13/12; A61K9/16;  
A61K9/50; B01J13/06; (IPC1-7): B01J13/00

**- european:** A61K9/16H6F; A61K9/50H6F2; A61K9/50H6F2B;  
A61K9/50P; B01J13/12

**Application number:** GBD1297476 19710419**Priority number(s):** DE19702010116 19700304**Also published as:**

 SU379074 (A1)  
 FR2084200 (A5)  
 ES388917 (A)  
 DE2010116 (A1)  
 CH549408 (A5)

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**Report a data error here****Abstract of GB1297476**

1297476 Microgranulate FARBENFABRIKEN BAYER AG 19 April 1971 [4 March 1970] 22308/71  
Heading A5B [Also in Division B8] Solid, free-flowing, substantially spherical particles (microgranulates) are prepared by dispersing or dissolving an "active" material in a solution of a cellulose ester in a glycol ether and introducing discrete droplets of the resultant into water whereby the glycol ether is given up to the water and the droplets become solidified and may be separated. Suitable cellulose esters are: cellulose acetate, propionate, propionate acetate and butyrate acetate preferably having 2.2 to 2.6 acyl radicals per anhydroglucose unit. Suitable glycol ethers are mono- and di-alkyl ethers of aliphatic glycols having 1 to 6 carbon atoms in the alkyl group. Examples relate to processes in which the "active" material is: aspirin, paraffin oil, TiO<sub>2</sub> and the compound (CH<sub>3</sub>O)<sub>2</sub>PO (CHOH-CCl<sub>3</sub>).

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## NO DRAWINGS

- (21) Application No. 22308/71 (22) Filed 19 April 1971  
(31) Convention Application No. P 20 10 116.0  
(32) Filed 4 March 1970 in  
(33) Germany (DT)  
(45) Complete Specification published 22 Nov. 1972  
(51) International Classification B01J 13/02 A61K 9/00  
(52) Index at acceptance  
B8C A  
A5B 763 764 766



## (54) A PROCESS FOR THE PRODUCTION OF MICROGRANULATES

(71) We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany of 509 Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the production of a microgranulate.

Microcapsules comprising hydrophobic or hydrophilic core substances and polymeric shells have recently been acquiring considerable interest because they enable the encapsulated core substances to be liberated under predetermined specific conditions.

Gelatin coacervates applied from aqueous media may be used as the shell material, in which case hydrophilic shells are formed.

Microcapsules with hydrophobic shells are more difficult to produce. Shells of this kind, however, are of particular interest for the encapsulation of water-soluble core substances. Capsules of this kind can be obtained by processes wherein the core material, in some instances even in the form of a solution, is dispersed in a solution of a capsule-forming polymer, and a second solvent is added to reduce the solubility of the polymer to such an extent that a polymer-rich phase (coacervate) is formed. This coacervate can envelop the dispersed particles or droplets so that, after isolation and drying, capsules with hydrophobic shells and, for example, hydrophilic contents are obtained. Suitable pairs of solvents combined with different polymers are described in British Patent Specification No. 931,148. Unfortunately, working with solvent mixtures of this kind is by no means rational and involves high costs. In addition, this process is restricted in its application because the solvents must be adapted to the core material.

In another known process for the production of capsules with hydrophobic shells, the

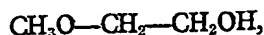
substances to be encapsulated are dispersed in a solution of a polymer which is suitable for shell formation, and the resulting dispersion is dispersed in a second liquid. The first liquid (solvent for the polymer) should not be miscible with the second liquid, whilst the polymer should not dissolve in the second liquid so that, when the polymer solution containing the dispersed core material is itself, dispersed in the second liquid, the polymer is precipitated and deposited on to the surface of the particles to be encapsulated (Dutch Patent Application 68 11852).

As can readily be demonstrated by experiments, the two solvents mix so quickly in practice that the polymer is precipitated in the form of filaments, lumps or strands and is no longer available for enveloping the dispersed particles. The Examples of Dutch Patent Application 68 11852 show that this can be prevented to some extent by dissolving in the second liquid a substance, for example even a polymer, which is able to enter into an interfacial reaction with the shell-forming polymer in the first liquid. In this way, the two solvents mix more slowly and useful capsule formation is possible. In this process, however, solvent mixtures contaminated by the shell-forming polymers are formed as secondary products, and they are difficult to work up.

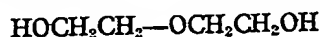
The present invention relates to a process for the production of a solid, free-flowing, substantially spherical microgranulate, wherein a solid or liquid material is dispersed or dissolved in a solution of a cellulose ester in a water-miscible glycol ether, discrete droplets of the resulting dispersion or solution are introduced into water, whereby the droplets harden due to loss of the glycol ether, and the substantially spherical microgranulate formed is separated.

Examples of water-miscible glycol ethers suitable for use in the process according to the invention include monoalkyl and dialkyl

ethers of aliphatic glycols, such as ethylene glycol, propylene glycol or butylene glycol, containing 1 to 6 carbon atoms in the ether alkyl group, ethylene glycol monomethyl ether



diethylene glycol



and ethylene glycol monoethyl ether.

Examples of suitable cellulose esters include esters of cellulose with one or more aliphatic monocarboxylic acids having preferably 1 to 6 carbon atoms, such as cellulose acetate, cellulose propionate and mixed esters such as cellulose propionate acetate or even cellulose butyrate acetate. The acyl contents of the cellulose esters preferably correspond to degrees of substitution of from 2.2 to 2.6 acyl radicals per anhydroglucose unit.

It was surprising that substantially spherical microgranulate particles having solid shells should be formed by the procedure according to the invention or, more generally, by introducing pre-formed particles of the organic phase into the aqueous phase.

The procedure according to the invention is limited to the glycol ether/cellulose ester system. If, for example, the cellulose ester is replaced by ethyl cellulose, it is not possible to obtain spherical particles, even when dispersions in water prepared therefrom are introduced in the form of preformed particles, since the particles expand and break up into fibres on entering water. The same happens when other solvents, for example ketones, are used instead of the aforementioned glycol ethers.

The process according to the invention can be carried out as follows: the starting material is a preferably 2 to 30% by weight, and most preferably 3 to 15% by weight, solution of the cellulose ester in the glycol ether. The core material to be encapsulated or embedded is dispersed or dissolved in this solution using the conventional mixers including, when dispersions are prepared, vibro-mixers, high speed stirrers and other homogenisers. The quantity of core material which is dispersed or dissolved is preferably from 30 to 90% by weight, based on the weight of polymer solution. In general, the quantitative proportions are selected in accordance with the required ratio between cellulose ester and encapsulated core material, because there are hardly any losses of polymer or core material in the process according to the invention. Amounts of cellulose ester of from 5 to 70% by weight, based on the microgranulates are sufficient for most applications.

Solid or liquid, hydrophobic or hydrophilic, inorganic or organic, substances can

be encapsulated or embedded by the process according to the invention. From this wide variety, the following groups of substances are mentioned by way of example; pharmaceuticals and plant-protection agents, foodstuffs and food additives (for example aroma substances or spices), odorants, dyes (for example inorganic or organic pigments, dye solutions or pastes), chemicals, lubricants and greases (for example oils), adhesives, and bonding agents. It is, of course, also possible to encapsulate mixtures of these substances.

Pre-formed particles of the dispersion or solutions of the core substance in the ethylene glycol ether/cellulose ester solution are introduced into water with gentle mixing by known means (e.g. stirrers or recirculating pumps). Preferably, the dispersions or solutions are initially sprayed in air, by means of single-component or two-component nozzles, so that preformed particles with a predetermined particle diameter are formed, and are subsequently introduced into the optionally stirred or mixed aqueous phase, which can also be part of a flowing system.

In the most simple instance of spraying by means of a single-component nozzle on to the surface of the water, it is necessary to select the favourable distance between the orifice of the nozzle and the surface of the water for the formation of spherical particles.

If the gap is too narrow, large and only partly coherent droplets are formed which readily burst on contact with the surface, so that the particle size distribution of the particles formed is very wide. If the gap is too large, deformed rather than spherical particles are formed.

The size of the primary particles is governed by the viscosity of the solution or dispersion from which they are produced (i.e. the type and quantity of solvent, cellulose ester and shell substance) and by the manner in which they are produced (in the case of spraying, for example, by the nozzle diameter and the spraying pressure).

The particles entering into the aqueous phase very quickly lose their solvent, accompanied by a decrease in the diameter of the primary particles. In general, residence times in pure water of from 5 to 10 minutes are long enough for most of the solvent to be transferred into the aqueous phase and for shell hardening to take place. With aqueous phases in which solvents are already present, the solvent is transferred slightly more slowly.

In principle, the operations described above can be carried out at temperatures of from 5 to 90°C, although as a rule they are carried out at temperatures of from 15 to 40°C.

After the shells have hardened to a sufficient extent, the spherical particles can be separated off from the water. They may

optionally be washed with more water in order to remove residual solvent, if any.

The separated particles are then dried, for example in a stream of air or even *in vacuo*, at a temperature of from 50 to 100°C. The drying conditions have to be adapted to the contents of the capsules (e.g. boiling point or melting point) to prevent the particles from being destroyed with consequent release of the core substance.

The spherical particles obtained contain the core material in the form of small droplets or particles embedded, or even to some extent dissolved, in the polymer. The size of the enveloped droplets or particles can be varied by control of the dispersion operation.

Core substances which were dissolved in the glycol ether are generally deposited in fine distribution during emergence of the solvent.

The size of the spherical particles, i.e. of the microgranulate, is governed by the aforementioned parameters. Particle sizes of from 50  $\mu$  to several millimetres can readily be obtained.

The microgranulates have a complete outer skin which can even be made porous with low polymer and high solvent contents.

The microgranulates produced in accordance with the invention have considerable significance in the administration or application of substances whose release is intended to be delayed (for example pharmaceuticals or plant protection agents) or which are intended to be released under special conditions such as, for example, pressure, temperature increase, or solvent addition.

#### Example 1

20 Parts by weight of acetyl salicylic acid were dissolved in a solution of 5 parts by weight of acetyl cellulose (molecular weight 9.10<sup>4</sup>, degree of substitution 2.5 acetyl groups per anhydroglucose unit) and 95 parts by weight of ethylene glycol monomethyl ether. This solution was added dropwise, by means of a nozzle having an internal diameter of 0.2 mm under a pressure of 1.5 atms., to 300 parts by weight of water, kept in gentle motion by means of a stirrer, the nozzle orifice being situated 15 cm above the surface of the water. The droplets entering the water (diameter approximately 1.5 to 2 mm) immediately became coated with a skin, and the solvent issued in the form of streaks. After a residence time of 30 minutes, the spherical particles were sifted off and dried in an air stream at 40°C.

25 Parts by weight of microgranulate with a particle diameter of 0.8 mm were obtained comprising solid, impervious shells which contained in their interiors fine acetyl salicylic acid crystals which were separated from one another by the polymer.

A microgranulate having an average particle diameter of 0.2 mm was obtained for a nozzle diameter of 0.15 mm and a spraying pressure of 3 atms.

#### Example 2 (Comparison).

The same solution as in Example 1 was poured into water with vigorous stirring rather than being added dropwise to water by means of a nozzle. Amorphous lumps, filaments and strands were formed. Some of the acetyl salicylic acid was transferred into the aqueous phase.

#### Example 3

8 Parts by weight of paraffin oil (droplet size 10 to 20  $\mu$ ) were emulsified by means of a high speed stirrer in a solution of 8 parts by weight of cellulose propionate acetate (molecular weight approximately 10<sup>5</sup>, propionate residues expressed as propionic acid 57%, acetyl residues expressed as acetic acid 5%) in 92 parts by weight of ethylene glycol monomethyl ether. This emulsion was introduced into 350 parts by weight of stirred water through a nozzle (internal diameter 0.2, spraying pressure 4 atms.) arranged at a distance of 20 cm. After 30 minutes, the spherical particles were separated off and dried in an air stream at 40°C. 16 parts by weight of microgranulate having an average particle diameter of 0.4 mm were obtained. The particles contained the oil droplets separated from one another by polymer walls.

#### Example 4

12 Parts by weight of titanium dioxide (particle size 20 to 40  $\mu$ ) were dispersed by means of a high speed stirrer in a solution of 6 parts by weight of cellulose butyrate acetate (molecular weight 7 to 8.10<sup>4</sup>, butyrate groups expressed as butyric acid 45%, acetyl groups expressed as acetic acid 20%) in 96 parts by weight of diethylene glycol (2,2'-dihydroxydiethyl ether). This dispersion was introduced into 200 parts by weight of water through a 0.5 mm nozzle arranged at a distance of 50 cm under a spraying pressure of 3 atms. After a residence time of 20 minutes, the spherical particles were separated off and dried *in vacuo* at 30°C.

18 Parts by weight of a microgranulate having a particle diameter of from 0.5 to 0.7 mm were obtained, containing the individual titanium dioxide particles embedded in the polymer matrix.

#### Example 5 (Comparison)

The procedure was as described in Example 1, except that ethyl cellulose (molecular weight 5.10<sup>4</sup>) was used as the polymer instead of the acetyl cellulose, under otherwise the same spraying conditions. It was

impossible to obtain microgranulate; instead, the droplets entering the water broke up and the polymer was precipitated in the form of fibres and strands.

5                                      Example 6  
(Comparison)

The procedure was as described in Example 3, except that butanone was used as the solvent. Spraying of the corresponding emulsion under the same conditions did not produce spherical particles with a solid shell; instead, the droplets broke up on entering the water and the polymer was precipitated in the form of strands and filaments.

15                                      Example 7

260 Parts by weight of the phosphorus compound



20 were dissolved in a solution of 40 parts by weight of acetyl cellulose (molecular weight of  $3.10^5$ , acetyl groups expressed as acetic acid 53%) in 700 parts by weight of ethylene glycol monomethyl ether, and the resulting solution was cooled to 0°C. This solution was introduced through a nozzle (internal diameter 1 mm, spraying pressure 1 atm.) from a height of 20 cm into 2000 parts by weight of water which were mixed and which had a temperature of 0°C. The spherical particles were separated off after a residence time of 25 minutes and dried *in vacuo* at 35°C. 98 Parts by weight of microgranulate having a particle diameter of 1.5 mm were obtained.

35                                      WHAT WE CLAIM IS:—

1. A process for the production of a solid, free-flowing, substantially spherical microgranulate, wherein a solid or liquid material is dispersed or dissolved in a solution of a cellulose ester in a water-miscible glycol ether, discrete droplets of the resulting dispersion or solution are introduced into water, whereby the droplets harden due to loss of the glycol ether, and the substantially spherical microgranulate formed is separated.

2. A process as claimed in claim 1 wherein the glycol ether is a monoalkyl or dialkyl ether of an aliphatic glycol having 1 to 6 carbon atoms in the alkyl group or diethylene glycol.

3. A process as claimed in claim 1 or 2 wherein the cellulose ester is an ester of cellulose with one or more aliphatic monocarboxylic acids having 1 to 6 carbon atoms.

4. A process as claimed in claim 3 wherein the cellulose ester is cellulose acetate, cellulose propionate, cellulose propionate acetate or cellulose butyrate acetate.

5. A process as claimed in any of claims 1 to 4 wherein the cellulose ester has from 2.2 to 2.6 acyl radicals per anhydroglucose unit.

6. A process as claimed in any of claims 1 to 5 wherein the solution comprises from 2 to 30% by weight of the cellulose ester in the glycol ether.

7. A process as claimed in claim 6 wherein the solution comprises from 3 to 15% by weight of the cellulose ester in the glycol ether.

8. A process as claimed in any of claims 1 to 7 wherein the quantity of core material is from 30 to 90% by weight, based on the solution of cellulose ester in glycol ether.

9. A process as claimed in any of claims 1 to 8 wherein the temperature is from 5 to 90°C.

10. A process as claimed in claim 9 wherein the temperature is from 15 to 40°C.

11. A process as claimed in claim 1 substantially as hereinbefore described.

12. A process as claimed in claim 1 substantially as described with reference to any of Examples 1, 3, 4 and 7.

13. Microgranulates when produced by a process as claimed in any of the preceding claims.

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